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Etiology of Childhood Otorrhea in Luanda, Angola, and a Review of Otitis Media in African Children

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ABSTRACT

Background: In resource-poor settings, otorrhea causes a significant burden of disease in children. Etiologic studies and structured data on otorrhea and chronic otitis media among African children remain scarce.

Methods: Here, we reviewed 678 bacteriologically analyzed otorrhea samples from Luanda Children's Hospital from children ≤15 years of age between 2008 and 2015. We then compared these to data from other studies among African children through a literature review of 20 papers published over two decades.

Results: Overall, 32 different bacteria were identified among 542 isolates from 654 children in Luanda. Gram-negative bacteria constituted the majority of all isolates (85%), whereby *Pseudomonas* sp was the most common (n = 158, 29%), followed by *Proteus* sp (n = 134, 25%). Among *Staphylococcus aureus* (n = 106, 10%), 69% of tested isolates were MRSA, and among *Enterobacteriaceae* 14% were ESBL isolates. Resistance to quinolones was rare. Furthermore, in a review of the literature, we found a high occurrence of otorrhea and chronic suppurative otitis media (CSOM) in children as well as possible gaps in existing knowledge.

Conclusions: In Angola, Gram-negative rods emerged as common causative agents of otorrhea in children followed by *S. aureus*. The magnitude of chronic otorrhea in Africa represents a cause for public health concern.

INTRODUCTION

Globally, ear infections commonly occur, whereby a child with otorrhea in Africa and in other resource-poor settings represents an everyday observation. An acutely draining middle ear may advance to chronic otorrhea, found in up to 6.6% of school children in Africa. (1) This prevalence exceeds the limit set by the World Health Organization (WHO), representing a massive public health concern. (2) While otitis media (OM) is generally well-characterized, data among African children remain scant. Only a few studies examined the youngest children, while studies of chronic suppurative otitis media (CSOM) in tertiary hospitals include patients across age groups, not simply children, who are most prone to ear infections. Limited recent data from Angola exist. (3, 4)

Because otorrhea is often neglected or deemed a minor problem, treatment is frequently delayed. Poverty, an important underlying factor, affects CSOM in multiple ways, including decreased host immunity and exposure to pathological organisms. In addition, parents' knowledge of ear infections, their health-seeking practices and the availability and quality of health services all link to poverty. (5) When otorrhea persists, complications such as hearing loss as well as extra- and intracranial complications can follow. (2) In Africa, CSOM stands as a major cause of preventable hearing loss and a typical mediator in OM-related mortality. (2, 6, 7)

In industrialized countries, *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* stand as the major pathogens linked to acute middle-ear infections. However, if infection persists and develops into CSOM, the etiology shifts towards a higher prevalence of Gram-negative strains. In general, few differences distinguish the etiologies when comparing developing and developed countries. (5) However, population and geographic-related variety appears to play a role in the etiology of otitis media. (8) For example, in Africa, *M.*

catarrhalis rarely causes AOM, whereas *Staphylococcus aureus* is common in both acute (9) and chronic (10) middle-ear infections. Bacteriological and susceptibility studies, particularly for middle-ear infections, are much needed in many countries, including low- and middle-income economies, given the risk for uncontrolled or inadequate antibiotic consumption. (11)

We, therefore, investigated the cause of ear discharge among young children treated in Luanda Hospital, a region with one of the highest incidences of AOM and CSOM in Africa. (7) We sought to identify the etiologic agents, changes among those agents over time and the associated antibiotic susceptibility patterns. To do so, we conducted a descriptive and retrospective laboratory-based study on draining ears in Luanda Children's Hospital, Angola, between 2008 and 2015. We also conducted a literature review on otorrhea and CSOM in children in Africa to situate our findings with current knowledge of the burden and etiology of these diseases among children across the continent.

MATERIALS AND METHODS

Data collection and analysis

Luanda Children's Hospital, a public and tertiary referral center, provides treatment to children ≤15 years of age primarily without referrals from the Angolan capital region. The population of Luanda is 2.8 million, an estimated 47% of whom are children <15 years. (12) Approximately 300 children are seen daily in the emergency department. With only a single public ear, nose and throat unit in Luanda, the majority of children experiencing ear problems are examined and treated at the children's hospital. Tympanocenteses are not performed routinely, although samples are taken from draining ears and analyzed by the hospital's microbiology laboratory (established in 2002). AOM is treated with amoxicillin with or without clavulanic acid or trimethoprim-sulfa. Otorrhea and CSOM are treated with available topical antimicrobials,

typically chloramphenicol, gentamycin, and —despite the expense and inconsistent availability—quinolones.

After receiving ethical approval from the hospital for our study, we collected otorrhea data from children ≤15 years between 2008 and 2015, including both inpatients and outpatients. Laboratory technicians took samples with a sterile swab after cleaning the ear canal with 60% alcohol. Ear pus was immediately inoculated on blood and chocolate agar plates and incubated in a 3%–4% CO_2 atmosphere for 24–48 hours. Bacteria were identified from positive cultures based on their colonial features, Gram-staining and standard phenotypic bacteriological methods. (13) Antimicrobial susceptibility was tested using available discs applying CLSI standards (14) and the inhibition zones were compared to those from control organisms. The laboratory request forms reported the susceptibility of each organism as sensitive, intermediate or resistant.

In this sample, we could not track the children's demographic characteristics given the lack of computerized information management systems in Angola. (15) However, previously (2004–2005, n = 375) laboratory data on ear pus samples provided estimates for a more specific age range. Data were analyzed using SPSS.

Literature review

Through a literature review, we aimed to answer two structured questions: First, what is the prevalence of OM in African children ≤15 years when CSOM and otorrhea are accepted? Second, what are the causative agents in these patients? We conducted a search (see Supplemental Digital 1, http://links.lww.com/INF/D376 for the specific search terms) of the Medline, African Journals OnLine, African Index Medicus and Cochrane databases for articles published between January 1997 and June 2017. Additionally, we manually searched citations in published papers and reviews. Figure 1 illustrates the study screening and selection processes.

The predefined protocol outlined the inclusion of studies describing the prevalence or etiologic agents or both in pediatric CSOM or otorrhea among at least 30 patients regardless of language of publication. Studies with a wider age range of participants were included if the results were reported separately for children ≤15 years of age. In addition, we reviewed and included publications assessing the burden of pediatric OM if the burden of disease was analyzed against children in the health-care setting.

RESULTS

Luanda Children's Hospital

In total, 678 samples were obtained from 654 children, of whom 296 (44%) were girls. In earlier years' ear pus samples (n = 375), children ranged in age from 2 weeks to 13 years, with the 5–95% age distribution ranging from 5 months to 7 years. The median age across all children reached 2 years. In our sample, bacteria were detected in 542 (80%) specimens, and the predominant isolate was registered. No growth was detected in 72 (11%) specimens, while 63 (9%) specimens were interpreted as contaminated and yielded no results. One sample was damaged.

In total, 542 isolates were identified representing 32 bacterial species (Table, Supplemental Digital Content 2, http://links.lww.com/INF/D377). *Pseudomonas* sp was the most common isolate (n = 158, 29%) followed by *Proteus* sp (n = 134, 25%), *S. aureus* (n = 106, 10%), *Klebsiella* sp (n = 36, 7%), *Escherichia coli* (n = 34, 6%), *Citrobacter* sp (n = 24, 4%) and *S. pneumoniae* (n = 21, 4%). The proportional detection rates of these and other etiologies remained relatively stable over time (Fig., Supplemental Digital Content 3, http://links.lww.com/INF/D378). Gram-negative bacteria constituted the majority of all isolates (85%), more specifically primarily comprising enteric rods (52%). Other pathogenic bacteria

were also found. *Salmonella* sp was detected in 14 children, *Shigella* in 7 children and *Yersinia* sp and zoonotic *Edwardsiella tarda* in 4 and 3 discharging ears, respectively. *Klebsiella ozaenae,* the causative organism of chronic nasal infections, was identified in 3 samples.

Antimicrobial susceptibility to at least three antibiotics was conducted for nearly all isolates (n = 536, 99%). Ciprofloxacin-resistant *Pseudomonas* sp remained rare, occurring in only 1% of strains. As expected, *Proteus mirabilis* was typically resistant to chloramphenicol in 78% of cases, whereas only 7% of strains showed resistance to ciprofloxacin. Among all *Enterobacteriaceae,* 14% were resistant to third-generation cephalosporins (ceftriaxone or cefotaxime) and were identified as expanded-spectrum β-lactamase (ESBL)–producing isolates, with the highest percentage for *E. coli,* 47% (7/15). Among *S. aureus,* 69% (18/26) were MRSA. *S. aureus* was resistant to chloramphenicol in 29% of samples and to ciprofloxacin in 4% of samples. Among the *S. pneumoniae* strains tested, 82% were sensitive to penicillin, while 93% were resistant to chloramphenicol. Table 1 summarizes the susceptibility results.

Literature review

Our literature search yielded 160 citations, of which we included 20 in our review (Figure 1). Among these, 12 publications provided data on the prevalence and the burden of disease, (1, 4, 16-25) while 8 publications included microbiological data.(26-33) Most studies consisted of hospital-based samples, whereas few population-based studies existed. Table 2 presents the findings for the prevalence, while Table 3 summarizes the etiological findings of otorrhea and CSOM among African children.

Prevalence and burden of otorrhea and CSOM

We found three large school-based studies (n = 969–13,109) (1, 17, 18) and one household survey (16) screening ears among unselected populations. In Nigeria, the prevalence of CSOM

ranged from 0% in an urban upper-class school to 6% among pupils in rural areas. (1) A household survey from the same country reported a 3% prevalence for CSOM. (16) In Kenya, CSOM occurred in 1.5% of children, typically in children under 6 years old and later in children 13–15 years old. (18)

Among HIV-positive children, otorrhea was common, occurring in up to 32% of patients. (19) Few papers examined otorrhea and CSOM in primary care settings, where CSOM affected up to 7% of attending children. Two studies from tertiary ENT units in Nigeria took a closer look at the burden of pediatric OM, accounting for 45% of all new ENT cases and 5% of all visits. (24, 25)

Etiology of otorrhea and CSOM

Only 8 studies met our inclusion criteria for etiological reporting (Table 3). The most common causative agents in otorrhea consisted of *Pseudomonas* sp (19–57%), *Proteus* sp (11–47%), *S. aureus* (5–40%) and *E. coli* (3–17%). By contrast, for CSOM, the causative agents included *Proteus* sp (22–43%), *Staphylococcus* sp (37%), *Pseudomonas* sp (13–15%) and *S. aureus* (5–14%). Only one laboratory performed fungal analysis (28), two anaerobic analysis (32, 33) and one mycobacterial cultures. (32) The antimicrobial susceptibility to fluoroquinolones was widely favorable for Gram-negative bacteria. (29, 32, 33)

DISCUSSION

Ear drainage among children in developing countries often yields Gram-negative rods. The most common Gram-positive organism found in Luanda was *S. aureus,* with *S. pneumoniae* and *H. influenzae* detected rather rarely. Thus, in our sample, Angolan children most likely suffered from chronic or recurrent discharge. Unexpectedly, *Salmonella* sp, *Yersinia* sp and *Edwardsiella*, were observed, findings not previously reported to the best of our knowledge. Our group,

however, previously identified a case of *Shigella* from ear discharge in the same laboratory in Luanda. (3) We assume that contaminated water, close contact between humans and animal feces and perhaps some traditional treatment practices (34) explain the variety of Gram-negative bacteria in our sample.

Furthermore, the pathogen spectrum in our cohort agrees with several other studies among African children (Table 3). In those studies, *Pseudomonas* and *Proteus* sp represented the most common isolates in otorrhea. *Proteus*, however, emerged as the most common isolate in Ethiopia, Zambia and in one study from South Africa. (26, 27, 32, 33) In our study, we found *S. aureus* in one-tenth of the isolates, typically detected in 5%–40% of otorrhea cases. (28, 29) While previous studies took into account a child's HIV status and sickle cell disease, no differences were found between the agents in HIV-positive and HIV-negative children. (4, 32) However, immunosuppression may still be an important factor as, for example, Tiedt et al. detected *Proteus mirabilis* more frequently among underweight children. (32)

Topical ciprofloxacin emerged as suitable treatment alternative for discharging ears, in agreement with current WHO guidelines for CSOM, since at least 93% of the four most common isolates were susceptible to it. While only half of the studies reviewed provided relevant information on antimicrobial resistance in children, susceptibility to quinolones remained high: for instance, 80% of all isolates in Zambia and 95% of Gram-negative and 93% of Gram-positive bacteria in South Africa. (9, 32) However, in Nigeria, the overall susceptibility rates were somewhat lower for quinolones. (28, 29)

MRSA commonly occurred in our series. In one study from South Africa, (9) no MRSA was detected from ear discharge, while other studies did not report its prevalence among children. Turning to ESBL, the 14% prevalence ESBL-producing *Enterobachteriaceae* reported

here agrees with rates of 23% for ESBL observed elsewhere in Africa. (35) Since susceptibility to carbapenems was not examined, we have no information regarding the potential carbapenemase-producing *Enterobacteriaceae* strains.

Our literature review identified only a few studies from Africa focusing or reporting specifically on children. In particular, children under the age of 5 remained underrepresented in population-based studies, and only a few studies were conducted in primary health care settings. In general, the role of poverty was clearly linked to CSOM since it significantly associated with a child's low socio-demographic status and their parent's education. (17) Similarly, persistent otorrhea associated with rural residency in one study (1) although such a clear difference was not observed in Kenya. (18) Since our review of the literature, two cross-sectional studies among children have appeared, providing estimates for otorrhea and CSOM. In rural Malawi among children 4–6 years old (n = 281), 5.4% suffered from CSOM. (36) In Rwanda among children under 5 (n = 810), middle-ear infections occurred in 5.8% of children with 2% showing signs of active otorrhea. (37) These studies underline the need for public health interventions.

While this study offers a clearer picture of CSOM in African children, we acknowledge several limitations to our study. Primarily, economic constraints presented one major obstacle to a more thorough study. An inadequate patient database from the hospital prevented a more detailed collection of patient data (including possible comorbidities), and we were unable to confirm the origin of otorrhea. In some cases, external otitis might have been included in our patient series. The age range from previous years likely matches our sample, since we expect no dramatic changes have occurred in the patient distribution during the period during which our sample was collected.

In addition, the Luanda microbiology laboratory lacked the facilities necessary for anaerobic, viral and fungal diagnostics. Furthermore, we could not culture mycobacteria, which also cause ear infections in Africa. Evidently, the role of mycobacteria appears minor, since we identified only one study with a single case of otogenic tuberculosis. (32) Still, we argue that the role of mycobacteria is underestimated in Africa since it is surging in areas with a high tubercular endemicity. (38) We also argue that the number of mixed infections in this study was likely underestimated. The number of otorrhea samples fluctuated greatly over time (Figure, Supplemental Digital Content 3, http://links.lww.com/INF/D378) likely stemming from periodic lack of resources—a rather common occurrence in Africa.

We limited our literature review to a few databases and only assessed data descriptively. However, to our knowledge, no previous review focused solely on African children. A review by DeAntonio et al. presented the epidemiology of OM in developing countries among children <5 years old, highlighting the global burden and prevalence of OM. (39) Their study included 15 African publications published between 1992 and 2011, which were primarily hospital rather than population based. That study showed a peak prevalence of OM among the youngest children.

Similar to the etiologies reported in other studies, our study indicates that Gram-negative rods are commonly present in otorrhea in Angola, whereas *S. aureus* remains the most common Gram-positive agent with a 69% representation of MRSA. Resistance to quinolones remains rare. Among all *Enterobacteriaceae*, 14% consisted of ESBL. Our literature review identified a limited number of studies focusing on the youngest children providing current estimates for CSOM. The prevalence of persistent otorrhea across studies seems sufficiently high to cause

concern among public health professionals. Thus, much greater attention should be paid to this mostly neglected child health issue.

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Figure 1. Flowchart of literature review from database and manual searches

List of Supplemental Digital Content

Supplemental Digital Content 1. Data search

Supplemental Digital Content 2. Table

Supplemental Digital Content 3 Figure

Table 1. Sensitivity of tested bacterial isolates* from ear pus samples from children in Luanda, Angola

	Penicillin	Amoxicillin	Chloramphenicol	Ciprofloxacin	Third-generation cephalosporin†	Ceftazidime	Gentamicin	TMP/SMX‡
Staphylococcus aureus	12/33 (36%)		24/34 (71%)	28/30 (93%)			12/18 (67%)	12/14 (86%)
Streptococcus pneumoniae	9/11 (82%)		13/14 (93%)	2/2 (100%)	6/7 (86%)			1/4 (25%)
Haemophilus influenzae		2/4 (50%)	0/4 (0%)		4/4 (100%)			0/3 (0%)
Pseudomonas sp				91/92 (99%)	43/54 (80%)	81/84 (96%)	69/91 (76%))	
Proteus mirabilis		17/44 (39%)	15/67 (22%)	55/59 (93%)	40/41 (98%)	0/36 (0%)	51/64 (80%)	17/59 (29%)
Klebsiella sp		2/8 (25%)	10/21 (48%)	26/28 (93%)	10/13 (77%)	10/13 (77%)	19/22 (86%)	9/23 (39%)
Escherichia coli		3/15 (20%)	3/16 (19%)	18/22 (82%)	8/15 (53%)	15/17 (88%)	14/23 (61%)	7/24 (29%)
All *Enterobacteriaceae*			47/162 (29%)	156/169 (92%)	95/110 (86%)			

*Isolates may have been tested for sensitivity to different antimicrobial agents.

†Ceftriaxone or cefotaxime

‡Trimethoprim-sulfamethoxazole

Table 2. Prevalence of otorrhea and CSOM among children aged ≤15 years in Africa among unselected and selected populations

Country, year, reference	Study setting, design	Age range	Diagnosis	Prevalence: n diagnosis / n children (%)
	Unselected population			
Nigeria, 2003 (1)	School, cross-sectional	8–15 years	CSOM	Rural 42/699 (6); urban 0/270 (0)
Nigeria, 2005 (16)	Household survey, cross-sectional	0–12 years	CSOM	15/600 (3)
Nigeria, 2008 (17)	School, cross-sectional	9–15 years	CSOM	35/1500 (2)
Kenya, 2015 (18)	School, cross-sectional	2–15 years	CSOM	203/13,109 (2)
	Selected population			
South Africa, 2007 (19)	HIV, primary care clinic, retrospective	7–45 months	Otorrhea	104/326 (32)
Nigeria, 2007 (20)	HIV, hospital, case-control	7 months–11 years	Otorrhea	28/258 (11)
Angola, 2011 (4)	HIV, hospital, case-control	9 monts–14 years	CSOM	HIV 21/78 (27); controls 3/78 (4)
			Dry perforation	HIV 7/78 (9); controls 1/78 (1)
Angola, 2012 (21)	SCD*, hospital, case-control	8 months–15	CSOM	Controls 2/61 (3)

		years	Dry perforation	SCD 1/61 (2)
South Africa, 2014 (22)	Primary care clinic, cross-sectional	2–15 years	CSOM	8/121 (7)
South Africa, 2014 (23)	Primary care clinic, cross-sectional	2–15 years	CSOM	9/180‡ (5)

*Sickle cell disease

†Lower respiratory tract infection

‡Ears

Table 3. Etiological studies on otorrhea and CSOM among African children ≤15 years old

Diagnosis	Country, year, reference	Study setting, design*	Data collection	Age range	n isolates / n samples / n children	Main pathogens identified n (%)
Otorrhea	Ethiopia, 2009 (26)	Laboratory Retrospective	2000–2008	2 months–15 years	256/315/315	*Proteus* 120/256 (47) *Staphylococcus aureus* 93/256 (36)
	Ethiopia, 2011 (27)	Laboratory Retrospective	2003–2010	2 months–14 years	331/354/354	*Proteus* 103/331 (31) *S. aureus* 75/331 (23) *Pseudomonas* 63/331 (19) *Escherichia coli* 56/331 (17)
	Nigeria, 2011 (28)	Laboratory Retrospective	NA	0–12 years	301/400/NA	*S. aureus* 116/289† (40) *Proteus mirabilis* 82/289 (28) *E. coli* 33/289 (11) *Streptococcus* sp 27/289 (9)
	Nigeria, 2011 (29)	Hospital Retrospective	2006–2007	0–15 years	61/65/65	*Pseudomonas* 35/61 (57) *Klebsiella* 10/61 (16)

						Proteus 7/61 (11) *S. aureus* and *Streptococcus pyogenes* each 3/61 (5)
	Nigeria, 2012 (30)	Laboratory Retrospective	12 months, 2010	0–14 years	59/59/60	*Pseudomonas* 29/59 (49) *S. aureus* and *Proteus* each 14/59 (24) *E. coli* 2/59 (3)
CSOM	Ethiopia, 2004 (31)	Hospital NA	14 months, 2002–2003	2 months–15 years	99/NA/92	*Proteus* 43/99 (43) *S. aureus* 14/99 (14) *Pseudomonas aeruginosa* 13/99 (13)
	South Africa, 2013 (32)	Hospital Prospective	17 months, 2009–2010	1–12 years	153/113/86	*Proteus mirabilis* 33/153 (22) *Pseudomonas aeruginosa* 22/153 (14) *Haemophilus influenzae* 22/153 (14) *Providencia* and *S. aureus* each 7/153 (5)
	Zambia, 2016 (33)	Hospital Retrospective	2014–2016	0–15 years	60/60/60	*Staphylococcus* sp 22/60 (37) *Proteus* 21/60 (35) *Pseudomonas* 9/60 (15) *Streptococcus* 4/60 (7)

*Data collection

†Etiologies reported among those isolates tested for antimicrobial susceptibility

Figure 1